Three New Flavonoids and Other Constituents from *Lonicera implexa*

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From the leaves of *Lonicera implexa* Aiton (Caprifoliaceae) 22 compounds (five iridoids, one saponin, one cyclitol, three quinic acid derivatives, and 12 flavonoids) were isolated and characterized. Three flavonoids, namely implexaflavone (**1**), madreselvin A (**2**), and madreselvin B (**3**), were new compounds. The structures were determined by spectroscopic methods, including 2D NMR. Some chemotaxonomic and ecological notes about the isolated compounds are given.

Lonicera implexa Aiton (Caprifoliaceae), known in Italy as "madreselva", is a herbaceous climber typical of the Mediterranean region, with an inflorescence of 2−6 reddish pink flowers.[1] The plant is not used in Italian folk medicine, although other species of the same genus (i.e., *Lonicera japonica* and *Lonicera hypoglauca*) are reported in the Chinese Pharmacopoeia. Moreover, the closest Italian species, *Lonicera caprifolium*, is used as a diuretic and for treatment of hepatitis and stomatitis.[2]

The studies on this genus deal mainly with iridoids and saponins, while flavonoids are less investigated; the species *L. implexa* has never been studied at all. This paper deals with the isolation and characterization of 22 substances belonging to various classes of compounds, in particular five iridoids, one saponin, one cyclitol, three quinic acid derivatives, and 12 flavonoids, three of which are new natural products.

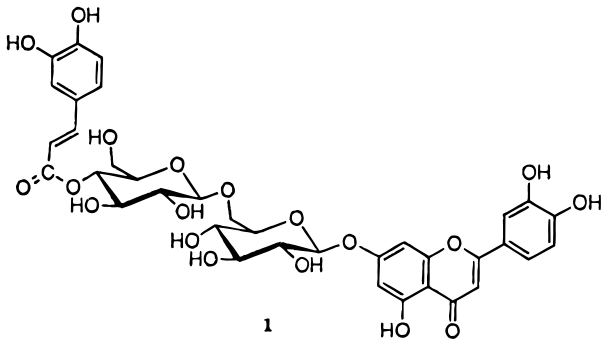
Results and Discussion

The dried leaves were extracted in a Soxhlet apparatus in turn with *n*-hexane, $CHCl_3$, $CHCl_3$−MeOH (9:1) and, at room temperature, with MeOH, obtaining the respective residues R_H, R_C, R_{CM}, and R_M.

Fractionation of R_{CM}, by size-exclusion chromatography and repeated column chromatography and preparative TLC over SiO_2, led to the isolation of 14 pure compounds. These were hederagenin 3-*O*-α-L-arabinopyranoside, epivogeloside, vogeloside, sweroside, loganic acid, ochnaflavone, myoinositol, apigenin 7-*O*-rutinoside, rhoifolin, grandifloroside, apigenin 7-*O*-primeveroside, apigenin 7-*O*-*β*-D-glucopyranoside, luteolin 7-*O*-*β*-D-glucopyranoside, and luteolin, which were identified by comparison of their physical/spectroscopic properties with literature reports.[3−6]

The residue R_M was suspended in MeOH−H_2O (7:3) and extracted, in turn, with EtOAc and *n*-BuOH, obtaining the residues R_{MAc} and R_{MBu}, respectively. From the former extract, after size-exclusion chromatography over Sephadex LH-20 with MeOH−H_2O (8:2), followed by RP-8 Lobar chromatography using H_2O−MeOH−HCOOH (6:4:0.1 or 7:3:0.1) as eluents, four pure compounds were isolated: chlorogenic acid methyl ester, implexaflavone (**1**), 3-methoxyquercetin 7-*O*-*β*-D-glucopyranoside, and macrantoin G. Known isolates were identified by comparison with literature data.[3,7,8]

The residue R_{MBu}, treated as R_{MAc}, gave a further four pure compounds, namely madreselvins A (**2**) and B (**3**), and the known compounds chlorogenic acid and luteolin 7-*O*-gentiobioside, identified by comparison of their NMR spectra with those of literature.[3,9] Compounds **1**, **2**, and **3** are new flavonoid glycosides.



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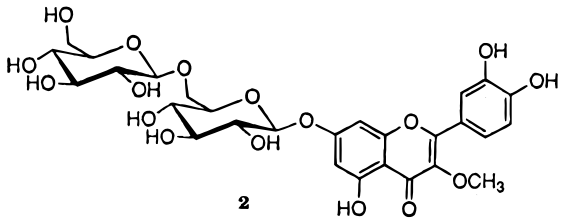

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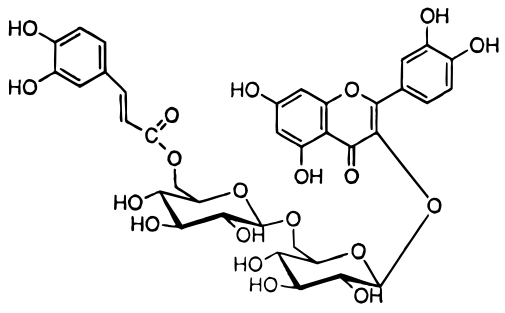

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Implexaflavone (**1**) was obtained as yellow amorphous powder that appears on TLC as an orange spot after

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treatment with Naturstoffereagenz A-PEG. The negative FABMS spectrum gave a molecular peak $[M - H]^-$ at 771 *m/z*, corresponding to the molecular formula $C_{36}H_{36}O_{19}$, supported also by elemental analysis (see Experimental Section). The ^{13}C-NMR spectrum shows 36 resonances, sorted by DEPT experiments in 2 CH_2, 21 CH, and 13 quaternary C. In the ^{1}H-NMR spectrum are present two broad singlets (δ 6.51 and 6.66), really two doublets with a very small *J* value as shown by COSY, typical of the two *meta*-related H-6 and H-8 protons of ring A of a flavonoid unit. The ABX system of ring B (δ 7.45, d, $J = 2.2$ Hz; 7.40, dd, $J = 8.3$, 2.2 Hz; 7.03, d, $J = 8.3$ Hz) and the H-3 singlet at δ 6.64 permit the identification of the aglycon as luteolin. A second aromatic ABX system (δ 6.83, d, $J = 1.6$ Hz; 6.71, dd, $J = 8.7$, 1.6 Hz; 6.69, d, $J = 8.7$ Hz), together with two coupled doublets ($J = 15.8$ Hz) at δ 6.16 and 7.38 and the signal of an ester C=O at δ 169.0, reveal the presence of a *trans*-caffeoyl moiety. The remaining 12 resonances of the ^{13}C-NMR spectrum of **1** are generated by two hexoses and exactly by two β-D-glucopyranoses 1→6 linked to form the disaccharide gentiobiose, as demonstrated by the downfield shift of the inner sugar methylene (C-6″). Because the downfield (1.5 ppm) and upfield shifts (1.0 and 2.8 ppm) of C-4‴, C-3‴, and C-5‴ of the outer glucose, it is possible to establish that the caffeoyl moiety is linked to C-4‴. The disaccharide is linked to the 7-OH on the basis of the typical glycosilation shifts experienced by the aglycon.[3] Therefore, **1** is 2-propenoic acid,3-(3,4-dihydroxyphenyl)-4″-ester with 2-(3,4-dihydroxyphenyl)-7-[(2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]-5-hydroxy-4*H*-1-benzopyran-4-one, or luteolin 7-*O*-β-D-glucopyranosyl(1→6)-[(4‴-*O*-caffeoyl)-β-D-glucopyranoside], which we named implexaflavone. This structure is confirmed by its negative FABMS spectrum where there are present, besides the molecular peak $[M - H]^-$ at 771 *m/z*, the peaks, respectively, due to the loss of the caffeoyl moiety $[M - H - 162]^-$ at 609 *m/z*, of an acylated glucose $[M - H - 324]^-$ at 447 *m/z*, demonstrating the linkage of the caffeic acid to the external hexose unit and of the acylated gentiobiose $[M - H - 486]^-$ at 285 *m/z*.

Compound **2**, madreselvin A, obtained as an amorphous yellow powder, presents in its negative FABMS spectrum a molecular peak $[M - H]^-$ at 639 *m/z*, corresponding to the molecular formula $C_{28}H_{32}O_{17}$, as confirmed by the elemental analysis; it gives a positive response (yellow-orange spot) to Naturstoffereagenz A-PEG. Its ^{13}C-NMR spectrum shows 28 resonances, sorted by DEPT experiments in 1 CH_3, 2 CH_2, 15 CH, and 10 quaternary C. The ^{1}H-NMR spectrum pattern of the aglycon moiety is very similar to that of **16**, but the absence of the singlet at about δ 6.6, joined to the lack of the methyne signal at about δ 104, permits the identification of the flavonol quercetin. The high resonance value of the methoxyl group (δ 59.7) suggests that the *ortho* positions should be substituted, so it must be placed at the 3 position.[3] Again, this situation is corroborated by the characteristic shifts observed for C-2, C-3, and C-4. Similarly to **16**, the sugar moiety can be identified as gentiobiose, and the site of glycosylation is the 7-OH. In the negative FABMS spectrum there are present, besides the molecular peak $[M - H]^-$ at 639 *m/z*, the peak due to the loss of a glucose $[M - H - 162]^-$ at 477 *m/z* and of gentiobiose $[M - H - 324]^-$ at 315 *m/z*. So compound **2** can be identified as quercetin 3-methyl ether 7-*O*-β-D-glucopyranosyl-(1→6)-*O*-β-D-glucopyranoside, a new compound that we have named madreselvin A.

The new compound **3**, madreselvin B, shows a molecular peak $[M - H]^-$ at 787 *m/z*; in its ^{13}C-NMR spectrum there are 36 resonances divided by DEPT experiments in 2 CH_2, 20 CH, and 14 quaternary C. Also, on the basis of elemental analysis, it is possible to calculate the molecular formula as $C_{36}H_{36}O_{20}$. The presence in the ^{1}H-NMR spectrum of the typical AB and ABX aromatic systems reveals that the aglycon is quercetin again. As with **1**, the signals of a *trans*-caffeoyl moiety and of a disaccharide identifiable as gentiobiose are discernible in its spectra. As shown by the downfield shift (about 2 ppm) of the methylene of the outer glucose unit, the acyl caffeoyl substituent is linked to the 6‴-OH. The site of glycosilation is the 3-OH of quercetin, as demonstrated by the upfield shift (about 3 ppm) of C-3 and the downfield shifts of C-4 (about 2 ppm) and C-2 (about 8.5 ppm). Thus, the structure of madreselvin B (**3**) is 2-propenoic acid,3-(3,4-dihydroxyphenyl)-6″-ester with 2-(3,4-dihydroxyphenyl)-3-[(2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]-5,7-dihydroxy-4H-1-benzopyran-4-one, or quercetin 3-*O*-β-D-glucopyranosyl(1→6)-[(6‴-*O*-caffeoyl)-β-D-glucopyranoside]. This structure is confirmed by its negative FABMS spectrum in which there are, besides the molecular peak $[M - H]^-$ at 787 *m/z*, the peaks due, respectively, to the loss of the caffeoyl moiety $[M - H - 162]^-$ at 625 *m/z* and of the acylated glucose $[M - H - 324]^-$ at 463 *m/z* which proves the linkage of the caffeic acid to the external hexose unit and of the acylated gentiobiose $[M - H - 486]^-$ at 301 *m/z*.

Among iridoids we have isolated five substances, four of which are secoiridoids. They are all biosynthetically correlated because they have as their common precursor loganic acid.[10] These compounds are also present in other species of *Lonicera*, but they have never been found in any other genus of the Caprifoliaceae; for this reason these secoiridoids could be considered as taxonomic markers of the genus. Only grandifloroside has been isolated for the first time from *Lonicera* and from the family.

We have also isolated 12 flavonoids, three of which are new natural compounds (**1**−**3**). Two substances, ochnaflavone and luteolin, are aglycons, while the other ones are glycosides. Ochnaflavone belongs to the class of biflavonoids, typical constituents of gymnosperms but with a limited and scattered distribution in angiosperms. Among these compounds, ochnaflavone is quite rare, and in the Caprifoliaceae it has been previously isolated only from *L. japonica*.[11]

It is worth mentioning that all the intermediates of the biosynthetic sequence of the new compound implexaflavone (**1**), from the aglycon through the derivatives 7-glucoside and 7-gentiobioside, have been isolated. Also the second new compound, madreselvin A (**2**), has been isolated, together with its 7-monoglucosilated precursor, another uncommon flavonoid. The acylation of many secondary metabolites generally represents one of the last steps of their biosynthesis. This kind of esterification is particularly important for flavonoids both for increasing their solubility in water (and hence to favor its lymphatic transport), and for protection of the

glycosides against the attack from the lithyc enzymes.[12] Thus, caffeoylation could be considered a protective event against parasitic insects that inject these enzymes with their saliva in order to break the glycosidic linkages and to suck the resulting sugar solution.

Finally, the three quinic acid derivatives are very important compounds for their inhibitory activity on lipid peroxidation in mitochondria and microsomes and on histamine release from mast cells, and therefore possess an antiinflammatory action. Furthermore, they seems to inhibit the HIV replication.[13]

Experimental Section

General Experimental Procedures. Melting points (uncorrected) were determined with a Kofler apparatus; optical rotations were measured on a Perkin-Elmer 241 polarimeter; FABMS were recorded, in the negative mode, with a VG ZAB instrument; ^{1}H- and ^{13}C-NMR were obtained with a Bruker AC200 spectrometer in CD_3OD, DMSO-d_6, and $CDCl_3$, using TMS as internal standard. All the 1D- and 2D-NMR experiments were performed using the standard Bruker library of microprograms; known compounds were identified by comparison of their spectral data with those of literature and, when available, by comparison with authentic samples. The following adsorbents were used for purification: flash chromatography, Merck Kieselgel 60 (230−410 mesh); low pressure chromatography, Merck Lobar Lichroprep RP-8 (31 × 2.5 cm); size-exclusion chromatography, Pharmacia Fine chemicals Sephadex LH-20; analytical TLC, Merck Kieselgel 60 F_{254}; the TLC cromatograms were visualized under UV at 254 and 366 nm and/or sprayed with Komarowsky or Naturstoffereagenz A-PEG reagents.

Plant Material. The flowered aerial parts were collected at Baia Domizia, Caserta, Italy, in June 1994. A voucher specimen is deposited in MI (Herbarium of the University of Milano).

Extraction and Isolation. The dried and ground aerial parts, deprived of the stems (975 g), were extracted successively in a Soxhlet apparatus with *n*-hexane, $CHCl_3$, $CHCl_3$−MeOH (9:1) (4 L × 20 h) and, at room temperature, with MeOH (2.5 L × 7 days × 3 times). After removal of solvents, *in vacuo* at up to 40 °C, the following residues were obtained: R_H (23 g), R_C (14 g), R_{CM} (61 g), and R_M (35 g).

R_{CM} was chromatographed on Sephadex LH-20 eluted with MeOH−$CHCl_3$ (4:1) (fractions A−K) obtaining, respectively, from fractions D, E, G, I, and K, after crystallization, ochnaflavone, myoinositol, luteolin 7-glucoside, and luteolin. From fraction E, chromatographed again on Sephadex LH-20 with MeOH−H_2O (85:15) as eluent (fractions E_1−E_{10}), compounds apigenin 7-primeveroside and apigenin 7-glucoside were yelded from fractions E_6 and E_8. From fraction E_5, after a new gel filtration on Sephadex LH-20 with MeOH−H_2O (1:1) and Si gel column chromatography with $CHCl_3$−MeOH−H_2O (7:3:0.3), compounds apigenin 7-rutinoside, rhoifolin, and grandifloroside were obtained. From fraction C of the first Sephadex LH-20 column, after repeated flash column chromatography, using $CHCl_3$−MeOH−H_2O (6:4:1 and 7:3:0.3) and $CHCl_3$−MeOH (9:1 and 7:3) as eluents, hederagenin 3-arabinoside, epivogeloside, vogeloside, sweroside, and loganic acid were purified.

R_M was suspended in MeOH−H_2O (7:3) and extracted, in turn, with EtOAc and *n*-BuOH obtaining, after removal of the solvents, the residues R_{MAc} and R_{MBu}. The former, after size-exclusion chromatography on Sephadex LH-20 MeOH−H_2O (4:1) (fractions A′−R′) and Si gel column chromatography with $CHCl_3$−MeOH (9:1) of fraction Q′, gave luteolin. Fraction F′, chromatographed on Lobar RP-8 eluted with H_2O−MeOH−HCOOH (7:3:0.1) gave chlorogenic acid methyl ester, while fraction H′ and L′, after being chromatographed on Lobar RP-8 with H_2O−MeOH−HCOOH (6:4:0.1), afforded **1**, 3-methoxy quercetin 7-glucoside, and macrantoin G.

The residue R_{MBu}, chromatographed on Sephadex LH-20 column with MeOH−H_2O (8:2) (fractions A″-R″) as eluent, gave **1**, **2**, luteolin 7-gentiobioside, and **3** after crystallization from fractions M″, F″, H″, and Q″ respectively. Fractions G″ and H″, chromatographed on Lobar RP-8 eluted with H_2O−MeOH−HCOOH (7:3:0.1 and 6:4:0.1, respectively), yielded chlorogenic acid and luteolin 7-gentiobioside.

Table 1. ^{13}C-NMR Spectral Data of **1**, **2**, and **3**

	compounds			
			3	
C	**1**[a]	**2**[b]	*a*	*b*
2	166.6	156.0[c]	158.4	156.3
3	104.2	137.9	135.6	133.3
4	183.9	178.1	179.4	177.3
5	162.8	160.9	162.9	161.2
6	101.6[c]	99.2	99.9	98.8
7	164.6	162.8	165.9	164.7
8	96.5	94.5	94.9	93.7
9	158.5	156.3[c]	158.9	156.4
10	106.8	105.9	105.8	103.8
1′	123.0	124.2	123.1	121.0
2′	114.4[d]	115.8[d]	116.5[c]	115.3[c]
3′	146.9[e]	145.2	145.9	144.9
4′	151.0	148.9	149.5[d]	148.7[d]
5′	117.0	115.7[d]	117.6	116.2
6′	120.6	120.7	123.1[e]	121.3[e]
1″	101.8[c]	99.7	104.0	101.0
2″	75.9	73.5	75.0	73.3
3″	78.1	76.7	78.0[f]	76.4
4″	70.9	70.1	71.3[g]	69.7
5″	77.9	75.4	77.6	76.3
6″	72.7	68.5	69.6	68.1
1‴	106.5	103.5	104.4	103.0
2‴	75.1	73.1	75.7	74.0
3‴	77.1	77.0	77.9[f]	76.4
4‴	72.4	69.3	71.5[g]	69.8[f]
5‴	75.1	76.3	75.0	73.5
6‴	62.9	61.1	64.6	63.3
1⁗	127.3		127.7	125.5
2⁗	114.6[d]		114.8	114.9
3⁗	146.4[e]		146.7	145.7
4⁗	149.4		149.8[d]	148.6[g]
5⁗	116.1		116.2[c]	115.8[c]
6⁗	123.8		123.6[e]	121.6[e]
C-α	114.9		115.2	113.8
C-β	147.2		147.2	145.3
C=O	169.0		169.2	166.6
OMe		59.7		

[a] Measured in CD_3OD. [b] Measured in DMSO-d_6. [c−g] Interchangeable signals.

Implexaflavone (1): yellow amorphous solid; *anal.* C 56.3%, H 4.9%, calcd for $C_{36}H_{36}O_{19}$, C 56.0%, H 4.7%; $[\alpha]^{20}_D$ −82.8° (*c* 0.12, MeOH); UV (MeOH) λ_{max} 252.8, 269.1 sh, 335.7; (MeOH + $AlCl_3$) 265.7, 298.0 sh, 360.4; (MeOH + $AlCl_3$ + HCl) 295.2 sh, 332.9 nm; ^{1}H NMR (CD_3OD) δ 4.44 (1H, d, J = 7.3 Hz, H-1⁗), 5.09 (1H, d, J = 7.1 Hz, H-1″), 6.16 (1H, d, J = 15.8 Hz, H-α), 6.51 (1H, br s, H-6), 6.64 (1H, s, H-3), 6.66 (1H, br s, H-8), 6.69 (1H, d, J = 8.7 Hz, H-5⁗), 6.71 (1H, dd, J = 8.7,

1.6 Hz, H-6‴), 6.83 (1H, d, J = 1.6 Hz, H-2‴), 7.03 (1H, d, J = 8.3 Hz, H-5′), 7.38 (1H, d, J = 15.8 Hz, H-β), 7.40 (1H, dd, J = 8.3, 2.2 Hz, H-6′), 7.45 (1H, d, J = 2.2 Hz, H-2′); ^{13}C-NMR spectral data, see Table 1; FABMS (negative) *m/z:* 771 $[M - H]^-$, 609 $[M - H - 162]^-$, 447 $[M - H - 324]^-$, 285 $[M - H - 486]^-$.

Madreselvin A (2): yellow amorphous solid; *anal.* C 52.9%, H 5.2%, calcd for $C_{28}H_{32}O_{17}$, C 52.5%, H 5.0%; $[\alpha]^{20}_D$ −58.8° (*c* 0.28, MeOH); UV (MeOH) λ_{max} 255.2, 270.1, 351.0 nm; ^{1}H NMR (DMSO-d_6) δ 3.78 (3H, s, OCH_3), 4.17 (1H, d, J = 7.5 Hz, H-1‴), 5.09 (1H, d, J = 6.9 Hz, H-1″), 6.49 (1H, J = 1.9 Hz, H-6), 6.78 (1H, d, J = 1.9 Hz, H-8), 6.93 (1H, d, J = 8.5 Hz, H-5′), 7.55 (1H, dd, J = 8.5, 1.8 Hz, H-6′), 7.60 (1H, d, J = 1.8 Hz, H-2′); ^{13}C-NMR spectral data, see Table 1; FABMS (negative) *m/z* 639 $[M - H]^-$, 477 $[M - H - 162]^-$, 315 $[M - H - 324]^-$.

Madreselvin B (3): yellow amorphous solid; *anal.* C 55.2%, H 4.9%, calcd for $C_{36}H_{36}O_{20}$ C 54.8%, H 4.6%; $[\alpha]^{20}_D$ −75.3° (*c* 0.02, MeOH); UV (MeOH) λ_{max} 251.8, 269.3 sh, 302.3 sh, 333.7; (MeOH + $AlCl_3$): 272.2, 303.5, 353.3, 423.1; (MeOH + $AlCl_3$ + HCl) 276.2 sh, 299.9, 327.4; ^{1}H NMR (CD_3OD) δ 4.18 (1H, d, J = 7.3 Hz, H-1‴), 5.22 (1H, d, J = 7.3 Hz, H-1″), 6.19 (1H, d, J = 2.1 Hz, H-6), 6.22 (1H, d, J = 16.0 Hz, H-α), 6.39 (1H, d, J = 2.1 Hz, H-8), 6.76 (1H, d, J = 8.1 Hz, H-5⁗), 6.88 (1H, d, J = 8.5 Hz, H-5′), 6.91 (1H, dd, J = 8.1, 1.8 Hz, H-6⁗), 7.02 (1H, d, J = 1.8 Hz, H-2⁗), 7.49 (1H, d, J = 16.0 Hz, H-β), 7.68 (1H, dd, J = 8.5, 2.0 Hz, H-6′), 7.75 (1H, d, J = 2.0 Hz, H-2′); ^{1}H NMR (DMSO-d_6) δ 4.10 (1H, d, J = 7.4 Hz, H-1‴), 5.36 (1H, d, J = 7.0 Hz, H-1″), 6.15 (1H, d, J = 1.9 Hz, H-6), 6.23 (1H, d, J = 15.9 Hz, H-α), 6.35 (1H, d, J = 1.9 Hz, H-8), 6.74 (1H, d, J = 8.1 Hz, H-5⁗), 6.83 (1H, d, J = 9.1 Hz, H-5′), 6.97 (1H, dd, J = 8.1, 1.7 Hz, H-6⁗), 7.03 (1H, d, J = 1.7 Hz, H-2⁗), 7.42 (1H, d, J = 15.9 Hz, H-β), 7.57 (2H, m, H2″ + H6″); ^{13}C-NMR spectral data, see Table 1; FABMS (negative) *m/z* 787 $[M - H]^-$, 625 $[M - H - 162]^-$, 463 $[M - H - 324]^-$, 301 $[M - H - 486]^-$.

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